# HPV vaccination in HIV infection,

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## Summary

Persons with HIV are at increased risk of HPV infection, HPV disease, and HPV-related cancers compared to HIV negative persons. In persons with HIV, immune responses to vaccination are often sub-optimal, and while these improve with ART, they often remain lower and decline more rapidly than in HIV-negative individuals. Although the evidence base to support the ***immunogenicity*** of HPV vaccines in HIV+ve persons is reasonable, the evidence base to support the ***efficacy*** of HPV vaccines in HIV+ve individuals is inconsistent. There is one study in HIV+ve men who have sex with men (MSM) which showed ***no effect***, and two other studies, one in HIV+ve women and one in HIV+ve adolescents that showed ***reduced effectiveness***. All these effectiveness studies used Gardasil 4 (G4). Two studies in HIV+ve persons have shown superior immunogenicity of Cervarix (which uses a TLR4 agonist adjuvant) compared to G4. Studies of Hepatitis B vaccines in HIV+ve persons have shown that either (i) increased number of doses (ii) increased vaccine dose, or (iii) TLR agonist adjuvanted vaccines, all produce increased immunogenicity compared to standard vaccine regimes. Therefore, questions remain as to optimal HPV vaccine regimes in HIV and further clinical trials with different HPV vaccine regimes are needed.

## HIV and HPV

HIV-1 is a retroviral infection that evolved ~ 120 years ago, and entered human populations > 60 years ago via a number of chimpanzee/gorilla–to-human cross-species transmissions[1], with the subsequent development of a worldwide pandemic. The key to the current degree of control of the pandemic was the development of triple antiretroviral therapy (ART), and its roll out to the developing world that began in the early 2000s. The most recent UNAIDS global estimates are that ~36.9 million are HIV-infected with ~19.5 million receiving ART.

Persons with HIV, even when effectively treated with ART have an increased risk and rate of HPV acquisition, more frequent carriage of multiple HPV types, and an increased rate of HPV-related disease including more rapid progression to malignancies[2]. Some of these increased risks may be 'behavioural' due to increased HPV exposure pre-HIV, or on-going higher risk behaviour post-HIV acquisition. However, a fundamental part of the increased risk is 'immunodeficiency virus-associated' due to B-cell, T-cell and NK-cell dysfunction, persistent inflammation, and persistent mucosal epithelial abnormalities[3].

HPV vaccines have proved to have outstanding safety, efficacy and effectiveness in healthy immunocompetent young persons. Standard vaccination regimes for young girls and boys (aged 9–14 yrs) have already reduced from the originally licensed three doses to two doses, and there is now growing interest and a portfolio of trials evaluating whether one dose of HPV vaccine may be sufficient to induce long lasting protection in young healthy subjects[4]. However, HIV often reduces responsiveness to vaccines and their effectiveness[2,5,6]. Even subjects who have been ART treated with suppressed viral loads for > 5 years show specific defects in memory T Follicular Helper cell function leading to reduced B cell responses[7]. However, these defects can be reversed *in vitro* by certain priming stimuli (e.g. anti-IL2, IL-21).

## HPV vaccines in HIV

According to our searches, there are only three published studies of the efficacy / effectiveness of HPV vaccines in persons with HIV[8-10]. A placebo-controlled RCT of the effectiveness of G4 in adults >26 yrs in preventing anal HPV was stopped early for futility[8]. The study enrolled 575 US subjects (82% male, median age 47yrs, IQR 41-52yrs, median CD4 606, 88% HIV VL <200) to receive G4 vaccine or placebo 1:1, stratified by sex and presence of anal biopsy HSIL. The 1* endpoint was vaccine efficacy (VE) against new persistent HPV 6,11,16,18 (qHPV) anal infection, ± single final visit detection. VE against new persistent anal qHPV was 22% (95% CI -31% to 53%) which was not significant. High baseline HPV seropositivity was noted, which suggests that VE may have been compromised by prevalent sub-clinical / latent infections not detected at study entry.

A Canadian study enrolled a cohort of 432 HIV+ve girls & women aged 9-65yrs (median age 39yrs, IQR 34-45yrs, median CD4 500, 69% HIV VL <50) to receive 3 doses of G4 vaccine[9]. Two hundred and seventy nine women met the inclusion criteria for the 2yr follow up efficacy analyses (95.3% of those received 3 doses), comprising 279 'intention to treat' (ITT), 270 'naïve to relevant type' (NRT), and 223 'per protocol' (PP - 3 doses, NRT, data > 7 month) populations. Incidence rates were: persistent qHPV 6/11/16/18 - ITT 2.3 /100py, PP 1.0 /100py; genital warts - ITT 2.3 /100py, PP 1.0 /100py. No cases of qHPV CIN2+ occurred in FU. The majority of the persistent qHPV in the ITT analysis was due to HPV18, and all cases in the PP analysis were due to HPV18. The persistent qHPV cases showed lower CD4 counts (median 333), but similar anti-VLP antibody levels as non-failure cases.

Comparison of rates of a combined endpoint of qHPV related infection and disease /100py with non-contemporary groups of qHPV vaccinated women and unvaccinated HIV+ve women aged 24-45yrs showed: vaccinated women without HIV - 0.1 /100py; vaccinated women with HIV – 1.2 /100py; unvaccinated women with HIV – 1.5 /100py.

A study of G4 vaccine effectiveness and HPV anti-VLP Ab levels in perinatally-HIV infected and uninfected youth has recently been accepted for publication[10]. This was a prospective observational cohort of (a) perinatally HIV infected (PHIV, n=310) and (b) perinatally HIV exposed, uninfected (PHEU, n=148) girls & boys, 90% (PHIV) and 78% (PHEU) of whom received G4 vaccination. The mean age at first dose & length of FU was, PHIV = 13.7 yrs, 3.5 yrs; PHEU = 12.4 yrs, 3.3yrs. 40% (PHIV) vs. 16% (PHEU) received at least 2 vaccine doses, and females were more likely to receive the full 3 dose course (46% PHIV, and 14% PHEU) compared with 6% and 0% of PHIV and PHEU males.

Seroconversion to HPV 6, 11, 16 and 18 occurred in 83%, 84%, 90%, and 62% of vaccinated PHIV compared to 94%, 96%, 99%, and 87% of vaccinated PHEU respectively, (P<.05 for all comparisons). GMTs were lower in the PHIV vs PHEU within each category of G4 doses received. Higher GMTs were associated with younger age, lower HIV-1 RNA viral load, and higher CD4 % at first G4 vaccination. Abnormal cytology occurred in 33 of 56 PHIV and 1 of 7 PHEU sexually active vaccinated females, yielding incidence rates per 100 person-years of 15.0 (10.9 to 20.6) and 2.9 (0.4 to 22.3), respectively. There were marginal associations between lower CD4 %, HIV RNA >1,000 & not on ART and abnormal cytology (p <0.10 >0.05), but not HPV Ab titre or number of doses. Genital warts occurred in 9 of 110 PHIV and 1 of 40 PHEU sexually active vaccinated females, yielding incidence rates per 100 person-years of 1.7 (0.9 to 3.2) and 0.6 (0.1 to 4.4), respectively.

All these three trials examining the effectiveness of HPV vaccines in HIV reflect patients receiving historic HIV treatment standards of care. That is, 78% of the adolescent HIV+ve cohort were born prior to 1998, and the median CD4 nadir in the Canadian female study was 230 and in the US / Brazil predominantly MSM study 256. Whether better effectiveness of HPV vaccines would be seen in patients who have started anti-retroviral therapy immediately after diagnosis is not known, but this should be investigated.

There have been a number of studies examining the immunogenicity of HPV vaccines in persons with HIV and, in general, there is some reduction in HPV VLP antibody levels compared to HIV negative subjects[10,11]. Better immunogenicity is seen when HIV viral replication is controlled, and when there is no overt immunodeficiency[2,12]. Longitudinal data suggests somewhat reduced antibody persistence[13,14], although modest memory B cell responses after G4 out to 4-5 years have been reported[13], and vaccinated HIV+ve subjects respond to late boosting with a 4th dose[14,15].

An alternative HPV vaccine to G4 is Cervarix, a bivalent HPV 16/18 vaccine that uses the adjuvant AS04, a combination of the traditional adjuvant alum plus the TLR4 agonist monophosphoryl lipid A. A trial from Sweden showed superior immunogenicity of Cervarix compared to G4 in HIV[16]. Ninety one HIV+ve subjects (61 men, 30 women, median CD4 590,

88% on ARVs) were randomized 1:1 to Cervarix or G4 vaccine. All Cervarix recipients seroconverted at 1yr to HPV16 & HPV18; >95% of G4 recipients seroconverted to HPV 6, 11, & 16 and 73% to HPV18. Both vaccines induced cross-reactive antibodies (Luminex pseudovirion assay), greater in women than in men, but the spectrum was wider for Cervarix (31, 33, 35, 45, 56, 58) than for G4 (31, 35, 73).

Recently the results of a 4–arm vaccine RCT in 257 HIV+ve (CD4 >350, women with both vertical and sexually transmission) & 289 HIV-ve women aged 15-25yrs were presented[17]. Both HIV +ve and HIV–ve women were randomised 1:1 to Cervarix or G4, and serology was measured using a pseudovirion-based neutralizing antibody assay. At 24 months Cervarix was superior to G4 in the HIV positive females, for HPV16 by 2.74 fold (CIs 1.83-4.11) and for HPV 18 by 7.44 (4.79-11.54) in GMTs. Both CD4 cell and B memory cells were assayed out to 12 months. In general, in HIV negative women, the cellular responses are similar to those of Einstein *et al*[18], and again, in general, the responses in HIV+ve women are similar to those in HIV-ve women in this study. However, the exception was memory B cell responses against HPV 18 in HIV+ve women receiving G4, which were poor with median responses of 0 across the whole 12 month period (Berlaimont V, personal communication). Interestingly these poor anti-HPV18 responses appears to be in keeping with the data of McClymont *et al*[9]. Memory B cell priming induced by G4 to HPV 16 was also poor after the 1st dose with a medians of 0 spots.

This data showing better immunogenicity in HIV with an additionally TLR agonist-adjuvanted vaccine compared to a classical alum-adjuvanted vaccine is in keeping with data obtained using different Hepatitis B virus (HBV) vaccines in HIV. The use of Fendrix (AS04 adjuvanted HBV vaccine) improves vaccine responses in HIV[2]. A randomised controlled trial of Engerix (alum-adjuvanted HBV vaccine) vs Engerix + a TLR9 adjuvant in HIV also showed superior immunogenicity of the TLR9-adjuvanted vaccine[19]. These data suggesting that TLR agonist-adjuvanted vaccines might produce better responses in HIV patients are in keeping with the description that the specific defects in memory T Follicular Helper cell function in HIV could be reversed *in vitro* by priming stimuli such as anti-IL2 & IL-21 that stimulate the same MyD88 cellular transcription pathways as TLR agonists[7].

Therefore, both the McClymont *et al* data and ongoing immune deviation under ART raise the possibility that the observed potential lack of effectiveness with G4 in HIV is due to impaired cellular immunity and helper function rather than solely impaired antibody production. This leads to consideration of whether the use of Cervarix, which might overcome the Tfh defect, might produce better HPV vaccine effectiveness outcomes in persons with treated HIV. However, the obvious drawback is that Cervarix does not contain HPV 6/11 VLPs. Interestingly, Cervarix has been shown to induce cross-reactivity in heathy girls / women with a vaccine effectiveness of 34.5% against persistent HPV 6/11 at 48

months[20], and also associated with a modest reduction in the incidence of genital warts in young girls in ecological observations[21]. However, this lack of solid protection against ano-genital warts & HPV 6/11 could be overcome by using by using a mixed vaccination schedule, with initial Cervarix priming, such as Cervarix / Gardasil / Cervarix, or Cervarix / Cervarix / Gardasil. Recent data suggests that such mixed HPV vaccine regimes are indeed safe, effective, and induce solid antibody responses against all the HPV types in Gardasil 9 (G9)[22].

In summary, in our opinion the lack of solid evidence of HPV vaccine effectiveness in HIV is of significant concern, and we propose that further clinical trials are needed.

## References


1. Worobey M, Gemmel M, Teuwen DE, Haselkorn T, Kunstman K, Bunce M, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature 2008;455:661-4
2. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015; http://www.bhiva.org/vaccination-guidelines.aspx
3. Tugizov S. Human immunodeficiency virus-associated disruption of mucosal barriers and its role in HIV transmission and pathogenesis of HIV/AIDS disease. Tissue Barriers 2016;4(3):e1159276
4. Kreimer AR, Herrero R, Sampson JN, Porras C, Lowy DR, Schiller JT, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine 2018;36:4774-82
5. Irungu E, Mugo N, Ngure K, Njuguna R, Celum C, Farquhar C, et al. Immune response to hepatitis B virus vaccination among HIV-1 infected and uninfected adults in Kenya. J Infect Dis 2013;207:402-10
6. Cohen C, von Mollendorf C, de Gouveia L, Naidoo N, Meiring S, Quan V, et al. Effectiveness of 7-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in HIV-infected and -uninfected children in South Africa: a matched case-control study. Clin Infec Dis 2014;59:808-18
7. Cubas R, van Grevenynghe J, Wills S, Kardava L, Santich BH, Buckner CM, et al. Reversible reprogramming of circulating memory T follicular helper cell function during chronic HIV infection. J Immunol 2015;195:5625-36
8. Wilkin TJ, Chen H, Cespedes MS, Leon-Cruz JT, Godfrey C, Chiao EY, et al. A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298. Clin Infec Dis 2018;67:1339-46

9. McClymont E, Lee M, Raboud J, Coutlée F, Walmsley S, Lipsky N, et al. The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living with HIV. Clin Infec Dis 2019;68:788-94
10. Moscicki AB, Karalius B, Tassiopoulos K, Yao TJ, Jacobson DL, Patel K, et al. Human papillomavirus (HPV) Ab levels & quadrivalent vaccine clinical effectiveness in perinatally-HIV infected and exposed, uninfected youth. Clin Infec Dis 2019 (in press)
11. Denny L, Hendricks B, Gordon C, Thomas F, Hezareh M, Dobbelaere K, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. Vaccine 2013;31:5745-53
12. Cespedes MS, Kang M, Kojic EM, Umbleja T, Godfrey C, Webster-Cyriaque JY, et al. Anogenital human papillomavirus virus DNA and sustained response to the quadrivalent HPV vaccine in women living with HIV-1. Papillomavirus Res 2018;6:15-21
13. Weinberg A, Huang S, Moscicki AB, Saah A, Levin MJ; IMPAACT P1085 Protocol Team. Persistence of memory B-cell and T-cell responses to the quadrivalent HPV vaccine in HIV-infected children. AIDS 2018;32:851-9
14. Weinberg A, Song LY, Saah A, Brown M, Moscicki AB, Meyer WA 3rd, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and non-vaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. J Infec Dis 2012;206:1309-18
15. Ellsworth GB, Lensing SY, Ogilvie CB, Lee JY, Goldstone SE, Berry-Lawhorn JM, et al. A delayed dose of quadrivalent human papillomavirus vaccine demonstrates immune memory in HIV-1-infected men. Papillomavirus Res 2018;6:11-4
16. Faust H, Toft L, Sehr P, Müller M, Bonde J, Forslund O, et al. Human Papillomavirus neutralizing and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. Vaccine 2016;34:1559-65
17. Folschweiler N, Teixeira J, Joshi S, Goldani L, Supparatpinyo K, Basu P, et al. End of study results of a 2 year multicountry phase IV randomized comparative study of the immunogenicity and safety of the AS04-HPV-16/18 vaccine and the HPV-6/11/16/18 vaccine in HIV-positive female subjects aged 15-25 years. EUROGIN Lisbon 2018, abstract 275
18. Einstein MH, Levin MJ, Chatterjee A, Chakhtoura N, Takacs P, Catteau G, et al. Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: follow-up through month 48 in a phase III randomized study. Hum Vaccin Immunother 2014; 10:12, 3455--3465

19. Cooper CL, Angel JB, Seguin I, Davis HL, Cameron DW. CPG 7909 adjuvant plus hepatitis B virus vaccination in HIV-infected adults achieves long-term sero-protection for up to 5 years. Clin Infec Dis 2008;46:1310-4
20. Szarewski A, Skinner SR, Garland S, et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against low risk HPV types (PATRICIA randomised trial): an unexpected observation. 2013;208:1391–6.
21. Howell-Jones R, Soldan K, Wetten S, Mesher D, Williams T, Gill ON, Hughes G. Declining genital warts in young women in England associated with HPV 16/18 vaccination: an ecological study. J Infect Dis 2013;208:1397-403
22. Gilca V, et al. Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine - A randomized clinical trial. Vaccine 2018;36:7017-24